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(54) **Synthesis of isoquinuclidine**

(57) A process for preparing isoquinuclidine in which a lower alkyl ester of p-aminobenzoic acid is first hydrogenated to form a cis and trans mixture of 4-aminocyclohexanecarboxylic acid alkyl ester on which there is first accomplished a reductive benzylation and then a cyclization to an amide which is then reduced to isoquinuclidine.

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The chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

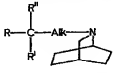
SPECIFICATION

**Synthesis of isoquinuclidine**

The present invention relates to the synthesis of 2-azabicyclo[2.2.2]-octane (isoquinuclidine) which has the following structural formula

and derivatives thereof.

Isoquinuclidine and pharmacologically acceptable salts thereof are known to be intermediates in the preparation of certain tertiary amines of the general formula



wherein Alk is a lower alkylene radical containing 2 to 6 carbon atoms; R represents lower alkyl containing 1 to 6 carbon atoms, phenyl, halophenyl, tolyl or pyridyl; R' represents lower alkyl containing 1 to 6 carbon atoms, phenyl, halophenyl, tolyl, pyridyl, cyano or hydrogen; R'' represents lower alkyl containing 1 to 6 carbon atoms, phenyl, halophenyl, tolyl, pyridyl or hydrogen; or R' and R'' may together be a doubly bonded oxygen atom or both may represent alkoxy groups containing 1 to 6 carbon atoms or together are an ethylenedioxy or propylenedioxy group. In particular, it is known that 2-azabicyclo[2.2.2.]octane hydrochloride is an intermediate in the preparation of 2,2-diphenyl-4-(2-azabicyclo[2.2.2]oct-2-yl)butyronitrile hydrochloride.

The preparation of said tertiary amines is described in U.S. Patent No. 4,088,234, the contents of which are incorporated herein by reference. Said tertiary amines are, themselves, intermediates in the preparation of useful compounds which are disclosed in U.S. Patents Nos. 3,772,300; 3,790,581; 3,843,646; and 3,847,923.

There are several processes for the preparation of isoquinuclidine disclosed in the prior art. In one known process, p-aminobenzoic acid hydrogenated to a mixture of cis and trans-4-aminocyclohexanecarboxylic acid. The cis-4-aminocyclohexanecarboxylic acid is then isolated by fractional crystallization and is first cyclized to 2-azabicyclo-[2.2.2]-octan-3-one (isoquinuclidone) by pyrolysis at 250—290°C and then reduced to isoquinuclidine.

It has been reported that in the above known process, the yield of cis-4-aminocyclohexane-carboxylic acid from the hydrogenation of p-aminobenzoic acid was improved to approximately 29.5% where the reaction was carried out over platinum, and the yield of isoquinuclidine from the reduction of isoquinuclidone over copper chromite was approximately 25—30%. The prior art also discloses that the reduction of p-aminobenzoic acid over a mixed metal (10% rhodium—0.1% palladium) catalyst affords a cis-trans mixture which is cyclized by heating in boiling Dowtherm A® (258°C) to give isoquinuclidone in 81—84% yield, (55—60% from p-aminobenzoic acid). It has also been reported that while isoquinuclidone is not reduced by lithium aluminum hydride in either, N-benzylisoquinuclidone, prepared from isoquinuclidone by alkylation with a sodium amide and benzyl bromide in approximately 74% yield, is reduced by lithium aluminum hydride in ether in 89% yield.

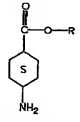
It is noted that one disadvantage of the processes of the prior art is that the entire cis-trans mixture of 4-aminocyclohexanecarboxylic acid resulting from the hydrogenation of p-aminobenzoic acid cannot be used. Other drawbacks associated with these processes result from the relatively low isolated yield of cis-4-aminocyclohexane carboxylic acid obtained, from the high temperature required to cyclize the cis-4-amino-cyclohexanecarboxylic acid, and from the relatively low yield in the reduction of isoquinuclidone to isoquinuclidine.

The present invention describes a new, improved synthesis process for the preparation of isoquinuclidine. Benzocaine or some other alkyl ester of p-aminobenzoic acid is first hydrogenated to form a cis and trans mixture of 4-aminocyclohexanecarboxylic acid ester on which there is first accomplished a reductive benzylation and then a cyclization to an amide which is then reduced to isoquinuclidine. Surprisingly and unexpectedly, it is found that the crude hydrogenation product may be cyclized, so that the need to isolate the cis isomer is avoided. It has also been found that the use of this reaction provides increased yields and permits milder reaction conditions.

As those familiar with the art will recognize, acid addition salts of isoquinuclidine are generally more stable than isoquinuclidine, itself. These salts may be conveniently stored until they are needed and may be converted to isoquinuclidine by neutralizing them with an appropriate basic solution.

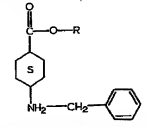
The invention therefore provides a process for the preparation of isoquinuclidine comprising the steps of:

(a) hydrogenating a lower alkyl ester of p-aminobenzoic acid to form a mixture of cis and trans isomers of a cyclohexyl compound having the formula



wherein R is an alkyl group having 1 to 4 carbon atoms;

(b) reductively benzylating the cyclohexyl compound to form a mixture of cis and trans isomers of a benzylated compound having the formula

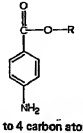


(c) cyclizing the benzylated compound to form N-benzyl-2-azabicyclooctan-3-one;

(d) reducing said N-benzyl-2-azabicyclooctan-3-one to N-benzyl-2-azabicyclooctane; and

(e) debenzylating said N-benzyl-2-azabicyclooctane to form the isoquinuclidine.

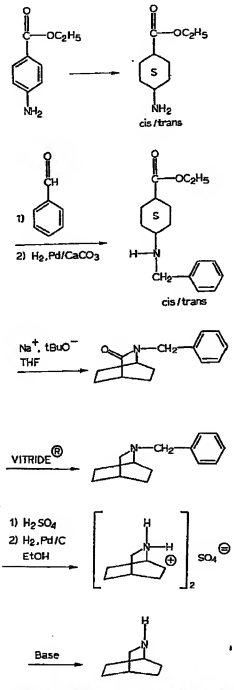
In carrying out the present invention, isoquinuclidine is prepared from a lower alkyl ester of p-aminobenzoic acid having the general formula



wherein R is defined as an alkyl group having 1 to 4 carbon atoms. An example of such an ester is ethyl-p-aminobenzoate (benzocaine), which is available commercially from a number of sources.

The benzocaine is hydrogenated in ethanolphosphoric acid mixture using a 5% Rh/C catalyst. The catalyst is removed by filtration and sufficient triethylamine is added to neutralize the phosphoric acid. The mixture is then treated with benzaldehyde and acetic acid, allowed to stand for a while, and then is hydrogenated using $Pd/CaCO_3$ catalyst. The resulting solution of the ethyl esters of cis and trans 4-N-benzylaminocyclohexanecarboxylic acid is freed of ethanol and the residue is made alkaline with cold aqueous potassium hydroxide solution. The N-benzylamino esters are isolated by extraction into 3:1 hexane:ethyl acetate and the solution is freed of solvent. Without purification, the crude ester mixture is treated with sodium t-butoxide (from sodium hydride and t-butyl alcohol) in THF (tetrahydrofuran) to form N-benzyl-2-azabicyclooctan-3-one. The crude lactam, as isolated from the reaction mixture, is reduced with sodium bis(2-methoxyethoxy)aluminum hydride (available from the Hexcel Speciality Chemical Co. under the trademarks, Vitride®) to N-benzyl 2-azabicyclooctane. The amine is purified by partitioning between aqueous hydrochloric acid and 4:1 ethyl acetate:hexane to effect removal of neutral contaminants (benzyl alcohol, mineral oil from the sodium hydride). The amine, as isolated from the aqueous acid, is neutralized with sulfuric acid in ethanol and the amine sulfate is debenzylated using hydrogen and Pd/C catalyst. Isoquinuclidine as the free amine is then obtained by treating the amine sulfate with an appropriate basic solution such as an aqueous solution of sodium hydroxide. Other acid addition salts can be made by treating the free amine with a variety of acids such as phosphoric, hydrochloric, hydrobromic, sulfamic, citric, lactic, succinic, tartaric, perchloric, acetic, benzoic, and related acids. This process is shown further in Scheme I as follows:

SCHEME 1




The following example illustrates the invention. In this example relative amounts are given in parts by weight, except as otherwise noted.

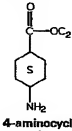
**Example**

**1. Hydrogenation of benzocaine**

100 g of benzocaine (0.6054 moles) and 20 g of 5% Rh/C catalyst are placed in a 2-liter hydrogenation bottle under nitrogen. A solution of 40.8 ml 85% phosphoric acid (0.60 mole) in 1.0 liter 3A ethanol (95%) is added to the solids. The system is purged with hydrogen and hydrogenation is performed at 60 psi (4.13 bar) hydrogen and 60—70°C. After 8 hours, hydrogen uptake has ceased and the mixture is cooled. The catalyst is removed by filtration and is washed with 3A ethanol to remove adhering product. (It should be noted that the spent catalyst may be pyrophoric and must be handled accordingly.) The filtrate is then concentrated back to a volume of about 1 liter under vacuum.

The catalyst employed for the above hydrogenation had been used four times previously. With fresh catalyst, hydrogenation occurs more rapidly and appears to give a slightly higher yield of the desired ester. The recovered catalyst should be washed with water and then 3A ethanol to remove occluded ammonium dihydrogen phosphate prior to reuse. The ammonium phosphate arises from partial hydrogenolysis of the amino group.

The product of this hydrogenation of benzocaine is a cis-trans mixture of ethyl 4-aminocyclohexane carboxylate which has the following formula:

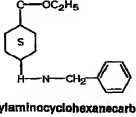


**2. Reductive benzylation of cis/trans ethyl 4-aminocyclohexane carboxylate**

65.4 g of triethylamine (0.647 moles, 89.9 ml) is added to the concentrated filtrate from the hydrogenation followed by 46.9 g of glacial acetic acid (0.781 moles, 44.7 ml). Benzaldehyde in the amount of 60.1 g (0.566 moles, 57.6 ml) is next added and the mixture is stirred at room temperature for 3 hours. The solution is then transferred to a 2-liter hydrogenation bottle containing 10 g 5% $Pd/CaCO_3$ catalyst and is hydrogenated at 5 psi (0.34 bar) and 25—30°C. The reduction is appreciably exothermic and some cooling is necessary at first. After 2.5 hours, hydrogen uptake has ceased and the catalyst is removed by filtration. Ethanol is distilled from the filtrate under vacuum (max. temp., 60°C).

The residue is dissolved in 250 ml water and a solution of 92.1 g (1.40 moles) 85% potassium hydroxide in 79 ml water is added slowly with good cooling and stirring; the temperature is kept below 28°C. An oil separates from the solution. The pH of the aqueous layer should be 11.0 (pH paper); if it is not more potassium hydroxide solution is added. The quantity of potassium hydroxide needed to bring the pH to 11 is less than would be calculated from the quantities of phosphoric and acetic acids originally present in the mixture. Some phosphoric acid is removed as the ammonium salt with the Rh/C catalyst and acetic acid probably distills along with the ethanol. Potassium carbonate must not be used in place of potassium hydroxide.

The oily product is extracted using three, 250-ml portions of 1:3 ethyl acetate:hexane. The combined extracts are dried over sodium sulfate, the solution is filtered, and the solvents are distilled from the filtrate under vacuum (ca. 25 mm at end of distillation). The residual oil weighs 153.9 g (97.3%). The NMR spectrum shows a ratio of $C_6H_5—CH_2—O—$ protons to $C_6H_5—CH_2—N—$ protons of 0.308. Assuming all benzylamino protons to be present as desired product, the ratio corresponds to a weight ratio of N-benzylamino ester to benzyl alcohol (formed from hydrogenation of excess benzaldehyde) of 88.7:11.3. A duplicate hydrogenation afforded 145.7 g of crude ester. The product of this reductive benzylation of cis-trans ethyl 4-aminocyclohexanecarboxylate is a cis-trans mixture of ethyl-N-benzylaminocyclohexanecarboxylate which has the following formula.

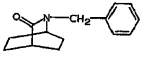


**3. Cyclization of cis/trans ethyl 4-N-benzylaminocyclohexanecarboxylate to N-benzyl-2-azabicyclooctane-3-one**

25.93 g (0.67 moles) of a 61.7% dispersion of sodium hydride in mineral oil is placed under nitrogen in a 1-liter, 3-neck flask fitted with a reflux condenser, stirrer, dropping funnel and thermometer. THF (79 ml) is added and the slurry of hydride is stirred and heated to gentle reflux. 45.73 g of t-Butyl alcohol (0.617 moles, 58.7 ml) is added gradually during 10 minutes, the addition rate being limited by the rate of hydrogen evolution; the mixture is then kept at reflux for an additional 10 minutes. The crude N-benzylamino ester obtained from 0.6054 mole of benzocaine, is dissolved in 135 ml THF and this solution is added slowly to the boiling sodium t-butoxide solution during about 65 minutes; the mixture foams somewhat at first. When the addition is completed, the mixture is stirred at reflux for an additional 5 hours. The reaction mixture remains homogeneous except for a little gelatinous material that collects as a ring above the solution. The mixture is cooled to 17°C under nitrogen and glacial acetic acid (38.2 ml, 0.668 mole) is added during 10 minutes, a gelatinous precipitate of sodium acetate separates. The precipitate is dissolved by addition of 135 ml water (pH of

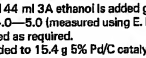
the aqueous layer is 7—8) and the THF is distilled from the mixture using an aspirator vacuum. The residual oil is extracted using 200 ml portion and two 150 ml portions of methylene chloride; the combined extracts are washed once with 150 ml brine and then dried over 20 g anhydrous sodium sulfate. The mixture is filtered and the filtrate is freed of solvents, finally under an aspirator vacuum. The residual soft solid weighs 118.6 g. This material is directly suitable for reduction with sodium bis(2-methoxy-ethoxy) aluminum hydride. It contains 9.9 g mineral oil; the mole ratio of benzyl alcohol to lactam is 1:3.96 (NMR).

The product of this cyclization of cis/trans ethyl 4-N benzylaminocyclohexanecarboxylate is N-benzyl-2-azabicyclooctan-3-one which has the following formula



**4. Reduction of N-benzyl-2-azabicyclooctane-3-one to N-benzyl-2-azabicyclooctane**

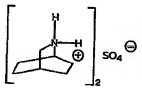
A 1-liter, 3-neck flask is fitted with a stirrer, reflux condenser, and dropping funnel. The flask is purged with nitrogen and 293.0 ml of sodium bis(2-methoxy-ethoxy)aluminum hydride (213.3 g, 1.055 moles) 70% in toluene) is added. To this is added 146.5 ml of THF with stirring; the temperature rises by 6—7°C. The solution is heated to reflux and a solution of the crude bicyclic amide (118.0 g) in 96 ml THF is added during about 50 minutes; the dropping funnel is rinsed with 20 ml of THF. The light-orange mixture is then kept at reflux (79°C) for 3 hours. The reaction mixture is cooled to about 4°C and a mixture of 75.5 ml each of water and THF is added during 40 minutes with cooling. A slight precipitate is present immediately following addition of the water, but within 5—10 minutes, the mixture has become gelatinous. Next, 140.4 ml of 6N hydrochloric acid (70.2 ml each of 12M hydrochloric acid and water) is added during 25 minutes. The gel thins rapidly and is replaced by a granular precipitate; the temperature is allowed to rise to 17°C. The mixture is stirred for 10 minutes and then is filtered through Celite; the solid is rinsed with three 150 ml portions of hot THF. The combined filtrates are then diluted with 250 ml hexane (Skellysolve B®) and washed with a solution of 40 g 85% potassium hydroxide in 400 ml water. The aqueous layer is discarded, the organic layer is dried over potassium carbonate, and the mixture is filtered. The filtrate is freed of solvents by distillation, finally under an aspirator vacuum. The residual oil weighs 105.4 g. The oil contains about 9.9 g mineral oil and about 12.1 g benzyl alcohol. For removal of the mineral oil and most of the benzyl alcohol, the crude amine is dissolved in a mixture of 368 ml ethyl acetate and 92 ml hexane (Skellysolve B®) (80:20 ratio of solvents). This solution is extracted with one 186.5 ml and one 20.7 ml portion of 3N hydrochloric acid (51.8 ml 12M hydrochloric acid+155.4 ml water); the mixture must be cooled during addition of the acid to absorb the heat of neutralization. The combined acidic extracts are kept cold and are made alkaline by careful addition of a solution of 81.8 g 85% potassium hydroxide (1.24 moles) in 82 ml water. The liberated amine is extracted using three 180-ml portions of 4:1 ethyl acetate:hexane. The combined extracts are dried over sodium sulfate, filtered, and the solvent is distilled from the filtrate, ultimately under an aspirator vacuum. The residual light-yellow oil weighs 84.7 g. This crude amine is directly suitable for debenzylation. It assays 90.9% by gas chromatograph. Evaporation of the ethyl acetate:hexane layer remaining from the extraction leaves a residue weighing 16.9 g. The product of this reduction of N-benzyl-2-azabicyclooctan-3-one is N-benzyl-2-azabicyclooctane which has the following formula



**5. Debenzylation of N-benzyl-2-azabicyclooctane**

Ethanol (3A, 95%) (240 ml) is placed in a 1-liter, 3-neck flask and stirred and cooled in an ice-bath as 11.6 ml (0.209 mole) of concentrated sulfuric acid is added. A solution of the crude N-benzylamine (84.2 g, 0.418 mole) in 144 ml 3A ethanol is added gradually with continued cooling. The resulting solution must have a pH of 4.0—5.0 (measured using E. Merck Indicator paper) if it does not, additional sulfuric acid should be added as required.

The amine sulfate solution is added to 15.4 g 5% Pd/C catalyst in a 1-liter hydrogenation bottle that has been flushed with nitrogen; 100 ml of additional 3A ethanol is used for rinsing purposes. Hydrogenation is performed at 50°C and 50 psi (3.44 bar) hydrogen pressure; reduction beings rapidly and is complete after 3 hours. The mixture is cooled and the catalyst is removed by filtration. The filtrate should have a pH of 5.0 or less; if not, add a little sulfuric acid as required. The ethanol is distilled under aspirator vacuum to leave a white, slushy solid that is held under vacuum for a while to remove as much residual solvent as possible. The solid weighs 64.2 g, and upon drying an analytical sample in an Abderhalden apparatus, the material loses about 13% of its weight. Most probably the weight loss is due to water that was in the ethanol. The product of this debenzylation of N-benzyl-2-azabicyclooctane is a salt of 2-azabicyclooctane (isoquinuclidine sulfate) having the formula



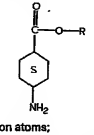
**6. Isolation of the free amine**

Crude, vacuum dried isoquinuclidine sulfate (20.0 g) is mixed with 35 ml water and a solution of 9.7 g sodium hydroxide in 10 ml water is added. The amine is extracted using two 100-ml. portions of diethyl ether and the combined extracts are dried over solid potassium carbonate. The solution is filtered and the filtrate is concentrated by distillation. The residue is then distilled at atmosphere pressure. Isoquinuclidine distilled at atmosphere pressure. Isoquinuclidine distills at about 170—175°C and condenses to a solid crystalline mass; about 8.0 g is obtained. The compound rapidly absorbs moisture and carbon dioxide when exposed to the atmosphere. The mediocre recovery (53%) is due to the high water solubility and high volatility of the compound. The isolated isoquinuclidine has the following formula.

**Claims**

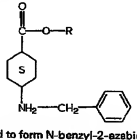
1. A process for the preparation of isoquinuclidine comprising the steps of:

(a) hydrogenating a lower alkyl ester of p-aminobenzoic acid to form a mixture of cis and trans isomers of a cyclohexyl compound having the formula



wherein R is an alkyl group having 1 to 4 carbon atoms;

(b) reductively benzylating the cyclohexyl compound to form a mixture of cis and trans isomers of a benzylated compound having the formula



(c) cyclizing the benzylated compound to form N-benzyl-2-azabicyclooctan-3-one;

(d) reducing said N-benzyl-2-azabicyclooctan-3-one to N-benzyl-2-azabicyclooctane; and

(e) debenzylating said N-benzyl-2-azabicyclooctane to form the isoquinuclidine.

2. A process as claimed in Claim 1 in which R is ethyl.

3. A process as claimed in claim 1 or claim 2 in which step (a) is carried out in an ethanol and phosphoric acid mixture over a rhodium/carbon catalyst.

4. A process as claimed in claim 3 in which the catalyst then is removed by filtration and sufficient triethylamine is added to neutralize the phosphoric acid.

5. A process as claimed in any of claims 1 to 4 in which step (b) is carried out by treatment with benzaldehyde and acetic acid after which hydrogenation over a palladium/calcium carbonate catalyst is accomplished.

6. A process as claimed in any of claims 1 to 5 in which step (c) is carried out by treatment with sodium t-butoxide in THF.

7. A process as claimed in any of claims 1 to 6 in which step (d) is carried out by treatment with sodium cis (2-methoxyethoxy) aluminum hydride.

8. A process as claimed in any of claims 1 to 7 in which after step (d) the N-benzyl-2-azabicyclooctane is purified by partitioning to effect removal of neutral contaminants and is then neutralized with sulfuric acid in ethanol.

9. A process as claimed in any of claims 1 to 8 in which step (e) is carried out by treatment with an acid and by hydrogenation over a mixed palladium/carbon catalyst to form an acid addition salt of isoquinuclidine.

10. A process as claimed in claim 9 in which the acid is sulfuric acid.

11. A process as claimed in claim 10 in which after step (e) the acid addition salt of isoquinuclidine is neutralized with a base to form isoquinuclidine.

12. A process as claimed in claim 1 substantially as herein described with reference to the example.

13. Isoquinuclidine when prepared by a process as claimed in any of claims 1 to 12.

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